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(54) **Title:** PHARMACOLOGICALLY ACTIVE SALTS

(57) **Abstract:** Novel salts formed between two active drug substances, wherein the first drug substance is an NSAID drug substance containing a carboxylic acid group and the second drug substance contains an amine group and is a local anaesthetic or selected from the group consisting of non-opioid analgesics, antipsychotics, antidepressants, narcotic antagonists and local anaesthetics. Such salts that are poorly soluble in tissue fluids are feasible for injectable prolonged release formulations where the NSAID additionally to minimize pain and tissue reaction at the site of administration.

WO 03/099293 A1

PHARMACOLOGICALLY ACTIVE SALTS

FIELD OF THE INVENTION

This invention relates to salts of drugs useful in the treatment and relief of pain (wounds, postoperative pain control, acute and chronic pain).

Salts of the present invention possess feasible solubilities in water and pharmaceutically acceptable organic solvents. They are formed from two drug substances where a NSAID (acid component) is used to form salts with e.g. a local anaesthetic agent (base component).

Drug delivery systems comprising salts according to the invention provide prolonged (controlled) release of the active components over a desired period of time periferically at the site of administration or centrally.

BACKGROUND OF THE INVENTION

In the field of topical, subcutaneous, intramuscular, intraarticur, epidural and spinal administration of active drug substances a need exists for pharmaceutical formulations, which allow the active substances be released in a controlled manner over a desired period of time. As regards pain management a particular need exists for formulations providing pain control over a desired prolonged period of time (about 24 hours or longer) and which minimise the potential of severe adverse events caused by burst absorption of the active substances into the systemic circulation. To achieve this goal a variety of experimental particulate (particle-based) drug delivery systems, such as microspheres, liposomes, crystal suspensions and the like, have been evaluated in the literature (Kohane et al., 2000; Le Corre et al. 1997, and references cited herein).

In the field of crystal suspensions some compounds exhibiting pamoic acid-like structures (aromatic ortho-hydroxy carboxylic acid structures) form poorly water-soluble salts with various drug substances containing an amine function group. However, the non-steroidal antiinflammatory drug diflunisal has not until this invention been used to form poorly water-soluble salts with pharmacologically active amines. Besides providing salts feasible for crystal suspensions or other types of precipitates, another advantage of the present invention is that combination therapy using e.g. diflunisal together with a local anaesthetic

agent has shown superior effect on pain relief by complementary effects and separate mechanisms thus resulting in a synergistic action at the surgical site (Chapman 1987).

Prior to the present invention a major disadvantage of commercially available aqueous solutions of local anaesthetics for injection is that such formulations are not able to provide prolonged drug release over a desired prolonged period of time. Thus, such formulations are suboptimal in postoperative pain control in areas of for example dental and joint surgery or the relief of pain caused by other types of tissue damage.

Another disadvantage of parenteral aqueous local anaesthetic therapy is that active substances are rapidly absorbed from the administration site into the systemic circulation with the risk that the patient experiences severe adverse events due to drug burst absorption.

In the case of for example joint surgery where postoperative therapy includes local administration of a local anaesthetic in combination with a non-steroidal-antiinflammatory drug (NSAID) still another disadvantage is that the NSAID has to be given orally in high doses, with the risk of development of unnecessary side effects, in order to obtain a therapeutic concentration at the diseased site.

As regards particulate (particle-based) drug delivery systems a major technological disadvantage is that such formulation types are difficult and therefore costly to manufacture (including the terminal sterilisation procedure). In addition, such formulations often suffer from poor physical stability.

DESCRIPTION OF THE INVENTION

As will be apparent from the above in the field of pain management there still is a need for developing and preparing drug delivery systems (such as, e.g., non-particle based formulations) comprising active substances which simultaneously provide both a local anaesthetic and an antiinflammatory effect, e.g. in a synergestic manner, in the vicinity of the administration site which enable controlled release of the active substances brought about by precipitation of poorly water-soluble salts of the active substances at the administration site (e.g. *in situ* crystal suspensions or other types of precipitates and which exert therapeutic action after administration by the topical, subcutaneous, intramuscular, intraarticular, epidural, or spinal route or to wounds or to surgically damaged tissue surfaces.

The present invention meets this need by providing poorly water-soluble salts of e.g. a local anaesthetic agent and a NSAID, such as, e.g. diflunisal, where the salts are incorporated in liquid pharmaceutical formulations for which the pharmaceutically acceptable vehicles might be modified in a manner to optimise the precipitation of the salts, and thus to optimise the dissolution and thereby the duration of action of the active substances in the vicinity of the administration site.

Thus, the present invention relates to a novel salt formed between two active drug substances, wherein the first drug substance is an NSAID drug substance containing a carboxylic acid group and the second drug substance contains an amine group and is a local anaesthetic.

In other aspects of the invention, the second drug substance is selected from the group consisting of non-opioid analgesics, antipsychotics, antidepressants, narcotic antagonists and local anaesthetics. Such salts that are poorly soluble in tissue fluids are feasible for injectable prolonged release formulations where the NSAID additionally acts to minimize pain and tissue reaction at the site of administration.

The NSAID drug substance forming part of a salt according to the present invention is selected from the group consisting of difunisal, sulindac, indomethacin, naproxen, fenoprofen calcium, ibuprofen, ketoprofen, indoprofen, tolmetin sodium, flurbiprofen, diclofenac sodium, mefenamic acid, flufenamic acid, fenclozic acid, alclofenac, bucloxic acid, suprofen, fluprofen, cinchophen, pirprofen, cinmetacin, acemetacin, ketorolac, clometacin, ibufenac, tolfenamic acid, fenclofenac, prodolic acid, clonixin, flutiazin, flufenisal, O-(carbamoylphenoxy)acetic acid, zomepirac sodium, niflumic acid, lonazolac, fenbufen, carprofen, tiaprofenic acid, loxoprofen, etodolac, alminoprofen, 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl) propionic acid, 4-biphenylacetic acid, 5-aminosalicylic acid, methothrexate, salazosulfapyridine, and azodisal sodium.

In specific embodiments, the second drug substance is a non-opioid analgesic selected from the group consisting of alfentanil, alphaprodine, anileridine, buprenorphine, butorphanol, dextromoramide, dextropropoxyphene, fentanyl, ketobemidone, meptazinol, methadone, pentazocine, pethidine, phenazocine, phenoperidine, and sufentanil.

In other embodiments, the second drug substance is an antipsychotic drug substance selected from the group consisting of haloperidol, haloperidol decanoate, risperidon, flupenthixol, olanzapine, fluphenazine, fluphenazine decanoate, zuclopenthixol

decanoate, and zuclopenthixole.

In further embodiments, the second drug substance is an antidepressant selected from the group consisting of amitriptyline, citalopram, escitalopram, fluoxetine, imipramine, sertraline, and paroxetine.

The second drug substance forming part of a salt of the invention may also be a narcotic antagonist selected from the group consisting of naloxone, naltrexone, and nalorphine.

In an especially interesting embodiment, the second drug substance is a local anaesthetic selected from the group consisting of amethocaine, chlorprocaine, etidocaine, lidocaine, bupivacaine, mepivacaine, prilocaine, ropivacaine, and procaine.

The water solubility of a salt of the present invention at a temperature of 21 °C is decreased with a factor of at least about 2.5 such as, e.g. at least about 5, at least about 7.5, at least about 10, at least about 15, at least about 20, at least about 25 or at least about 30 compared to the water solubility at a temperature of 21 °C of the hydrochloride salt of the amine component (i.e. the second drug substance of the salt of the present invention). Accordingly, the salt is not readily soluble in body fluids and upon administration the salt will only slowly dissolve and thereby release the drug substances during a prolonged period of time.

A salt according to the present invention may be in crystalline, amorphous or any polymorphous form.

A salt according to the present invention may be a salt, wherein at least one of the first and second drug substances is stereoactive and is present in racemic or any of its enantiomeric forms.

To further illustrate the invention the following gives a description of specific salts formed with diflunisal as an example of a NSAID substance. As appears from the above, the invention is not limited to a specific NSAID substance and therefore the following is intended to illustrate but not limit the invention.

Diflunisal salts active in pain control and relief of pain

Salts of the present invention active in pain control and the relief of pain are salts which may exhibit various polymorphic forms and which are formed from the NSAID (e.g.

diflunisal) and a pharmacologically active substance containing a primary, secondary, or tertiary amine functional group.

The said pharmacologically active substances containing an amine functional group which can be used to form salts with diflunisal may be selected without limitations among racemic or enantiomeric forms of those belonging to the following groups:

non-opiod analgesic drugs such as, e.g., buprenorphine, fentanyl, and the like;

antipsychotic drugs such, e.g., haloperidol, risperidon, flupenthixol, olanzapine, fluphenazine and the like;

antidepressant drugs such as, e.g., citalopram, fluoxetine, sertraline, paroxetine and the like;

narcotic antagonists such as, e.g., naloxone, nalorphine and the like;

local anaesthetic drugs such as, e.g., etidocaine, lidocaine, bupivacaine, mepivacaine, prilocaine, ropivacaine, procaine and the like;

In a specific embodiment of the invention, salts of a NSAID and a local anaesthetic is of specific interest.

Pharmaceutical formulations

A salt according to the present invention may be for oral, parenteral, topical or nasal use.

Accordingly, a salt according to the invention may together with one or more pharmaceutically acceptable excipients be formulated to a pharmaceutical composition.

Pharmaceutically acceptable excipients for use in pharmaceutical compositions according to the invention are well known to a person skilled in the art and can be found in standard text book such as, e.g., Remington's Pharmaceutical Sciences.

Pharmaceutical compositions may be in the form of e.g. tablets, capsules, sachets, powder, granules, pellets and comprise pharmaceutically acceptable excipients like e.g. diluents, fillers, disintegrants, binders, lubricants, glidants, etc.

The compositions according to the invention may be in the form of solutions, dispersions, emulsions, suspensions and comprise suitable dispersion media or solvents like e.g. water, oil etc. The compositions may further comprise suspending agents, solubilizers, preservatives, antioxidants etc.

They may also be in the form of e.g. creams, ointments, hydrogels, gels, lotions, plasters, bandages, sutures, sprays, transdermal delivery systems etc.

Commercially available conventional injectable suspensions providing prolonged duration of action can be divided into two groups: aqueous suspensions and oil suspensions. In the former case the duration of action is governed by the rate of dissolution of the solid salt particles at the administration site with the dissolution rate being influenced by the solubility of the salt in the tissue fluid and total surface of the particles (Zuidema et al., 1988). As regards oil suspensions dissolution of the salt in the oil phase or partition into the aqueous tissue phase may be the rate determining step in the release proces (Schultz, 1997). Similar in vivo release mechanisms at the administration site are operating for aqueous and oil suspensions formed in situ according to the present invention.

Formation of in situ aqueous crystal suspensions or other types of precipitate formulations of salts of the present invention is accomplished by dissolving the individual salt in a pharmaceutically acceptable organic solvent miscible with water or an organic vehicle comprising a mixture of water-miscible pharmaceutically acceptable organic solvents. Upon dilution with the aqueous tissue fluid of such relatively concentrated organic solutions of the salts, the salts will precipitate at the site of administration.

Formation of "in situ oil-like" crystal suspensions or other types of precipitate formulations of salts of the present invention is accomplished by dissolving the individual salt in an pharmaceutically acceptable organic vehicle comprising an oil and one or more organic solvents, the latter characterized by being at least partly miscible with both water and the oil. Upon contact with the aqueous tissue fluid of such relatively concentrated mixed solutions of the salts, the organic solvent will participate into the aqueous phase. Consequently the salts will precipitate in the oil phase.

In this context the term "pharmaceutically acceptable organic solvent" denotes organic solvents, such as, e.g. ethanol, 1-propanol, 2-propanol, propylenglycol, polyetylene glycols (PEG´s), dioxolanes, such as solketal, dimethylacetamide, and tetrahydrofuran.

In this context the term "oil" denotes oils, such as, e.g. vegetable oils and heavy mineraloils. Examples of vegetable oils include, but not limited to, almond oil, castor oil, fractionated coconut oil, cod liver oil, corn oil, cottonseed oil, glyceryl trioleate, linseed oil, Lipiodol, olive oil, palm oil, palm kennel oil, peanut oil, persic oil, poppyseed oil, rapseed oil, soybean oil, sunflower oil, sesame oil, teaseed oil, and hydrogenated vegetable oils. Further included are solid vegetable oils or fats in the melted state, such as, e.g. glyceryl monostearate, glyceryl distearate, glyceryl tristearate and glyceryl tripalmitate. Still further included are also synthetic oils, such as, e.g. ethyl oleate, isopropyl myristate, propylenglycol diesters, diethyl sebacate, polyoxyl castor oil, hydrogenated polyoxyl castor oil, and structured di- and triglycerides. The specifications of the said oils are in accordance with those stated in official monographs.

The proportions of the individual organic solvents or oils used in mixed organic vehicles may vary dependent on the physicochemical characteristics of the particular salt in question and the desired properties of the precipitate formed in situ. In the mixed organic vehicles each of the organic solvents or oils might be used in the range 0.1-99% v/v and preferably in the range 1-90% v/v. Especially preferred mixed organic vehicles are mixtures obtained by mixing an organic solvent with another organic solvent or an oil selected from ethanol, 1-propanol, 2-propanol, propylene glycol, solketal, N,N-dimethylacetamide, fractionated coconut oil, sesame oil, castor oil, ethyl oleate, and isopropylmyristate. Dependent on the oil solubility of the individual salt the amount of the solubility enhancing organic solvent, selected from ethanol, 1-propanol, 2-propanol, propylene glycol, solketal, N,N-dimethylacetamide and the like, has to be varied adequately.

By exploiting the common ion principle, further optimisation of the therapeutic performance of formulations such as, e.g., *in situ* crystal or other types of solid material suspensions according to the present invention, e.g. onset of action and duration of action, is obtained from dissolving a mixture of two or more salts of the present invention and/or excess amount of NSAID such as, e.g., diflunisal in an organic solvent or a mixed organic vehicle. Likewise excess amount of the amine component comprising the second drug substance of the salt of the present invention might be feasible. From salt solubility product considerations variation of excess of one of the components comprising the salt

can be used to vary the actual concentration of the other component comprising the salt at the administration site.

The concentration of a salt or a combination of salts of the present invention optionally combined with an excess amount of the specific NSAID substance (e.g. diflunisal) or the pharmacological active amine component of the salt in such organic solvents or mixed organic vehicles depends on the individual active substances comprising the salt(s), their potencies, the severity of the disease to be prevented or treated, the age and condition of the patient. Methods applicable to selecting relevant concentrations of a salt in an organic solvent or mixed organic vehicle are well known for a person skilled in the art and may be performed according to established guidelines for good clinical practice (GCP) or Investigational New Drug Exemption ("IND") regulations. A person skilled in the art would by use of methods described in textbooks, guidelines and regulations as well as common general knowledge within the field be able to select the exact dosage regimen to be implemented for any selected salt and dosage form using merely routine experimentation procedures.

Legends to figures

Fig. 1. In vitro dissolution profiles obtained, by using the rotating dialysis cell model with deionised water as the acceptor phase, after spiking different amounts of the bupivacaine-diflunisal salt dissolved in ethanol into approx. 3.8 ml water in the dialysis cell. The different pharmaceutical formulations: (i) 4.4 mg salt in 1.0 ml ethanol (bupivacaine-diflunisal salt does not precipitate in the dialysis cell), (n = 3); (ii) 30.9 mg salt in 1.2 ml ethanol (n = 3), and (iii) 57.9 mg salt in 1.2 ml ethanol (n = 2). Experiments performed at 37°C.

Fig. 2. In vitro dissolution profiles obtained, by using the rotating dialysis cell model with water as the acceptor phase, after spiking different amounts of the bupivacaine-diflunisal salt dissolved in 1.2 ml Viscoleo-ethanol (1:1 v/v) into approx. 3.8 ml water in the dialysis cell. The different pharmaceutical formulations: (i) 4.4 mg salt in Viscoleo-ethanol (1:1 v/v) (bupivacaine-diflunisal salt does not precipitate in the dialysis cell), (ii) 30.7 mg salt in Viscoleo-ethanol (1:1 v/v), and (iii) 60.3 mg salt in Viscoleo-ethanol (1:1 v/v).

Fig. 3. ^{13}C MAS NMR spectrum of lidocaine as a free base.

Fig. 4. ^{13}C MAS NMR spectrum of bupivacaine as a free base.

Fig. 5. ^{13}C MAS NMR spectrum of diflunisal.

Fig. 6. ^{13}C MAS NMR spectrum of a physical mixture of lidocaine as a free base and diflunisal.

Fig. 7. ^{13}C MAS NMR spectrum of a physical mixture of bupivacaine as a free base and diflunisal.

Fig. 8. ^{13}C MAS NMR spectrum of lidocaine-diflunisal salt.

Fig. 9. ^{13}C MAS NMR spectrum of bupivacaine-diflunisal salt.

Fig. 10. DSC thermogram of bupivacaine-diflunisal salt recrystallised from 50% v/v ethanol.

Fig. 11. DSC thermogram of bupivacaine-diflunisal salt recrystallised from 80% v/v 2-propanol.

Fig. 12. IR spectroscopy (conventional KBr method) on a Perkin Elmer 681 spectrophotometer of bupivacaine-diflunisal salt recrystallised from 50% v/v ethanol.

Fig. 13. IR spectroscopy (conventional KBr method) on a Perkin Elmer 681 spectrophotometer of bupivacaine-diflunisal salt recrystallised from 80% v/v 2-propanol.

Fig. 14. Thermogravimetric analysis on a Perkin Elmer TGS-2 and hot stage microscopy of bupivacaine-diflunisal salt recrystallised from 50% v/v ethanol.

Fig. 15. Thermogravimetric analysis on a Perkin Elmer TGS-2 and hot stage microscopy of bupivacaine-diflunisal salt recrystallised from 80% v/v 2-propanol.

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Materials and apparatus used in the examples

Materials

Bupivacaine hydrochloride Ph.Eur and lidocaine Ph.Eur were obtained from Unikem (Copenhagen, Denmark). Diflunisal was a gift from Dumex-Alpharma (Copenhagen, Denmark). Fractionated coconut oil (Viscoleo®) was purchased from Broeste (Copenhagen, Denmark). Sesame oil, castor oil and isopropyl myristate were delivered from Sigma (St. Louis, MO,

USA). Chemicals for preparing of buffers and HPLC mobile phases were of analytical grade. Demineralised water was used throughout. Visking dialysis tubing size 27/32, 21.5 mm with a cut off at 12-14.000 Da was employed for the dialysis cell.

Synthesis of salts

A. Liberation of bupivacaine free base from the hydrochloride salt

Bupivacaine hydrochloride 5 g (14.6 mmol) was dissolved in 250 ml water. Under stirring 4 N NaOH was added until pH reached 10.8. The precipitate was washed with water and dissolved in 50 ml ethtyl acetate. The organic phase was washed twice with 25 ml water. After drying ($NaSO_4$) the reaction mixture was evaporated to dryness in vacuo yielding a solid material (mp 106-107 °C). After recrystallisation (for example from ethyl acetate-

petroleum ether; acetone-water; 2-propanol-water) bupivacaine free base was obtained in high yield. Mp: 107-108 °C (107-108 °C, Merck Index).

B. Synthesis of the diflunisal salts of bupivacaine, lidocaine and morphine

The bupivacaine-diflunisal (Bupi-Dif) and lidocaine-diflunisal (Lido-Dif) salts were usually obtained by mixing amounts of lidocaine or bupivacaine base dissolved in a suitable organic vehicle such as acetone, ethanol, methanol, and the like with an equimolar amount of diflunisal dissolved in a suitable organic vehicle such as acetone. After evaporation of the organic solvent in vacuo the resulting solid was recrystallised from a suitable solvent pair.

The salts were identified by CHN analysis and HPLC.

CHN analysis of Bupi-Dif: found C: 68.97, H: 6.70, N: 5.20
calculated: C: 69.12, H: 6.74, N: 5.20

CHN analysis of Lido-Dif: found: C: 66.70, H: 6.22, N: 5.73
calculated: C: 66.92, H: 6.24, N: 5.98

HPLC experiments revealed no additional peaks and the salts were considered to exhibit a satisfactory purity. From the ^{13}C NMR experiments of diflunisal salts of lidocaine and bupivacaine (Figs. 3-9) it was confirmed that the solid materials were salts, thus excluding that the solid material consisted of a physical mixture of bupivacaine (or lidocaine) and diflunisal.

Bupivacaine diflunisal salts recrystallised from different media were furthermore characterised by DSC using a Perkin Elmer DSC-6 apparatus (Fig. 10 and 11), IR spectroscopy (conventional KBr method) on a Perkin Elmer 681 spectrophotometer (Fig. 12 and 13), Thermogravimetric analysis on a Perkin Elmer TGS-2 (Fig. 14 and 15) and hot stage microscopy. From the latter data it cannot be ruled out that polymorphs of the bupivacaine diflunisal salt might exist.

HPLC analyses

The Merck Hitachi system (L-6000A pump and L-4000 UV detector) was equipped with a 20 :l injection loop. The column used was an Inertsil ODS-2 column (250 x 4.6 mm, 5 :m particles). The flow rate was set at 1 ml min^{-1} and the column effluent was monitored at

264 nm. For diflunisal the mobile phase consisted of: acetonitrile: 0.1% phosphoric acid (7:3 v/v) which was made 10^{-3} M with respect to triethylamine. In case of bupivacaine and lidocaine analysis the mobile phase consisted of: acetonitrile: 0.1% phosphoric acid (2:8 v/v) which was made 10^{-3} M with respect to triethylamine.

Solubility experiments

Solubility experiments were carried in water, phosphate buffer pH 6.0-7.4 (I=0.445) and various organic vehicles at ambient temperature (20-21°C) or 37± 0.2°C. Excess of salt was added to the solvent and the mixture was rotated at the specified temperature until equilibrium was attained (72 hours). An 5 ml aliquot of the supernatant was withdrawn, filtered (discarding the first 2 ml) and after appropriate dilution the concentrations of both bupivacaine (or lidocaine) and the corresponding counter-ion diflunisal were determined by HPLC. The reported solubilities are the average of two determinations.

In vitro dissolution experiments

The dissolution studies were performed at 37°C by using a rotating dialysis cell previously characterised (Larsen et al., *Eur. J. Pharm. Sci.* (2000), 11, 223-229 and Fredholt et al., *Eur. J. Pharm. Sci.* (2000), 11, 231-237). The dialysis cell, containing 5-5.5 ml of the in situ formed crystal suspension, was lowered into 1000 ml of the release medium (deionised water). The revolution speed of the cell was set at 50 rpm. At appropriate intervals 5 ml samples were withdrawn from the aqueous release medium by using an autosampler. The samples were analysed by HPLC. Sampling was continued until equilibrium and in most cases the final concentration of the salt in the release medium was less than 0.2 times the saturation solubility of the salt (sink condition approximately maintained). The data is presented as the amount of drug released (M_t) in percent of the amount initially added to the dialysis cell, into the aqueous release medium. In the calculation the data has been corrected for sampling.

In situ formation of crystal suspensions or other types of precipitates and the dissolution of the active substances from such precipitates were assessed from adding a known volume of a solution of the salt in an appropriate organic vehicle to a well-defined volume of water in the dialysis cell.

EXAMPLE 1

Preparation of the diflunisal salt of bupivacaine

Bupivacaine free base 0.5 g (1.73 mmol) was dissolved in 10 ml acetone and diflunisal (0.43 g, 1.73 mmol) dissolved in 10 ml acetone was added. The reaction solution was left for 3 hours at ambient temperature. Acetone was removed by evaporation in vacuo. The resulting solid was recrystallized from 80% aqueous 2-propanol yielding the bupivacaine-diflunisal salt crystalline salt in a satisfactory yield. Basic characteristics of the said salt are given in Section: "Materials and apparatus used in the examples".

EXAMPLE 2

The compound in Example 1 was also prepared by procedures identical to that described in Example 1 except from that the crude solid salt was recrystallized from other solvents or solvent pairs such as, e.g., water-ethanol mixtures. Basic characteristics of the salts are given in Section: "Materials and apparatus used in the examples".

EXAMPLE 3

The compound in Example 1 was also prepared by procedures identical to that described in Example 1 except from that instead of acetone other organic solvents such as, e.g., ethanol, methanol and the like were used to dissolve bupivacaine free base and diflunisal, respectively.

EXAMPLE 4

The compound in Example 1 was also prepared by dissolving an amount of bupivacaine hydrochloride in water. This solution was added to an aqueous solution (pH 8.0) containing an equimolar amount of diflunisal. After mixing the pH of the reaction mixture was adjusted to pH 5-7 by using a suitable alkali hydroxide or an strong acid solution. The precipitated salt was isolated and recrystallized as described in Examples 1 and 2.

EXAMPLE 5

Preparation of the diflunisal salt of lidocaine

The crude diflunisal salt of lidocaine was obtained by mixing equimolar amount of diflunisal and lidocaine free base according to the procedures described in Examples 1 and 3. The crude salt was recrystallised according to the procedures described in

Examples 1 and 2. Basic characteristics of the diflunisal-lidocaine salt are given in Section: "Materials and apparatus used in examples.

EXAMPLE 6

Solubility behaviour of the diflunisal salts of bupivacaine and lidocaine

Solubilities of bupivacaine-diflunisal (Bupi-Dif) and lidocaine-diflunisal (Lido-Dif) salts in water and 0.2 M phosphate buffers (I = 0.45) were determined at 21 °C. Solubilities (expressed as mg salt/ml) have been determined from separate HPLC analyses of local anaesthetic and diflunisal, respectively, in the aqueous phase at equilibrium.

	pH 6.7	pH 7.4	water
Bupi-Dif (from diflunisal)	0.31	0.33	0.41
Bupi-Dif (from bupivacaine)	0.31	0.32	0.45
Lido-Dif (from diflunisal)	1.64	1.70	1.94
Lido-Dif (from lidocaine)	1.63	1.81	2.23

Estimates of the solubility of bupivacaine diflunisal salt in organic solvents/mixed organic vehicles (room temperature or 37 °C):

Above 100 mg/ml

- ethanol
- N,N-dimethylacetamide
- solketal
- 1-propanol

Between 40 and 100 mg/ml

- propyleglycol
- 2-propanol
- PEG 200
- Viscoleo-ethanol (1:1 v/v)
- Viscoleo-solketal (1:1 v/v)
- Viscoleo-N,N-dimethylacetamide

EXAMPLE 7

Preparation of pharmaceutical formulations providing bupivacaine-diflunisal salt in situ aqueous crystal or other types of solid material supension formulation

Such pharmaceutical formulations contain the bupivacaine-diflunisal salt dissolved in a pharmaceutical acceptable organic solvent such as, e.g., ethanol, 1-propanol, 2-propanol, N,N-dimethylacetamide, solketal, propylenglycol or polyethylene glycols, or mixed organic vehicles comprising such organic solvents . As an example, Figure 1 shows that the in vitro dissolution time (assessed by using the rotating dialysis model) for the in situ formed aqueous crystal or other types of solid material suspensions of the bupivacaine-diflunisal salt can be modified by using different concentrations of the bupivacaine-diflunisal salt in the ethanol solution. For the purpose of comparison is included the release profile from a ethanolic solution containing the bupivacaine-diflunisal salt (4.4 mg bupi-dif), from which no precipitation in the dialysis cell occurs.

EXAMPLE 8

Preparation of pharmaceutical formulations providing bupivacaine-diflunisal salt in situ "oil-like" crystal or other types of solid material suspension formation

Such pharmaceutical formulations contain the bupivacaine-diflunisal salt dissolved in a pharmaceutical acceptable mixed organic vehicle comprising an oil or a mixture of oils such as, e.g., fractionated coconut oil including Viscoleo®, castor oil or hydrogenated castor oils, and and one or more organic solvents such as, e.g., ethanol, 1-propanol, 2-propanol, polyethylene glycols or N,N-dimethylacetamide. As an example, Figure 2 shows that the in vitro dissolution time (assessed by the rotating dialysis cell model) for the in situ formed "oil-like" crystal or other types of solid material suspensions of the bupivacaine-diflunisal salt can be modified by using different initial bupivacaine-diflunisal salt concentrations in the mixed organic vehicle consisting of Viscoleo-ethanol (1:1 v/v).

CLAIMS

1. A salt formed between two active drug substances, wherein the first drug substance is an NSAID drug substance containing a carboxylic acid group and the second drug substance contains an amine group and is selected from the group consisting of non-opioid analgesics, antipsychotics, antidepressants, narcotic antagonists and local anaesthetics.

2. A salt according to claim 1, wherein the NSAID drug substance is selected from the group consisting of difunisal, sulindac, indomethacin, naproxen, fenoprofen calcium, ibuprofen, ketoprofen, indoprofen, tolmetin sodium, flurbiprofen, diclofenac sodium, mefenamic acid, flufenamic acid, fenclozic acid, alclofenac, bucloxic acid, suprofen, fluprofen, cinchophen, pirprofen, cinmetacin, acemetacin, ketorolac, clometacin, ibufenac, tolfenamic acid, fenclofenac, prodolic acid, clonixin, flutiazin, flufenisal, O-(carbamoylphenoxy)acetic acid, zomepirac sodium, niflumic acid, lonazolac, fenbufen, carprofen, tiaprofenic acid, loxoprofen, etodolac, alminoprofen, 2-(8-methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl) propionic acid, 4-biphenylacetic acid, 5-aminosalicylic acid, methothrexate, salazosulfapyridine, and azodisal sodium.

3. A salt according to claim 1 or 2, wherein the second drug substance is an analgesic selected from the group consisting of alfentanil, alphaprodine, anileridine, buprenorphine, butorphanol, dextromoramide, dextropropoxyphene, fentanyl, ketobemidone, meptazinol, methadone, pentazocine, pethidine, phenazocine, phenoperidine, and sufentanil.

4. A salt according to claim 1 or 2, wherein the second drug substance is an antipsychotic drug substance selected from the group consisting of haloperidol, haloperidol decanoate, risperidon, flupenthixol, olanzapine, fluphenazine, fluphenazine decanoate, zuclopenthixol decanoate, and zuclopenthixole.

5. A salt according to claim 1 or 2, wherein the second drug substance is an antidepressant selected from the group consisting of amitriptyline, citalopram, escitalopram, fluoxetine, imipramine, sertraline, and paroxetine.

6. A salt according to claim 1 or 2, wherein the second drug substance is a narcotic antagonist selected from the group consisting of naloxone, naltrexone, and nalorphine.

7. A salt according to claim 1 or 2, wherein the second drug substance is a local anaesthetic selected from the group consisting of amethocaine, chlorprocaine, etidocaine, lidocaine, bupivacaine, mepivacaine, prilocaine, ropivacaine, and procaine.

8. A salt according to any of the preceding claims, wherein the water solubility of the salt at a temperature of 21 °C is decreased with a factor of at least about 2.5 such as, e.g. at least about 5, at least about 7.5, at least about 10, at least about 15, at least about 20, at least about 25 or at least about 30 compared to the water solubility at a temperature of 21 °C of the hydrochloride salt of the second drug substance (the amine component).

9. A salt according to any of the preceding claims in crystalline, amorphous or any polymorphous form.

10. A salt according to any of the preceding claims, wherein at least one of the first and second drug substances is stereoactive and is present in racemic or any of its enantiomeric forms.

11. A salt according to any of the preceding claims, wherein the first drug substance is diflunisal and the second drug substance is a local anaesthetic.

12. A salt according to any of the preceding claims for use in medicine.

13. A salt according to any of the preceding claims wherein the first drug substance is diflunisal and the second drug substance is bupivacaine.

14. A salt according to any of the preceding claims wherein the first drug substance is diflunisal and the second drug substance is lidocaine.

15. A pharmaceutical composition comprising a salt according to any of claims 1-14 and a pharmaceutically acceptable excipient.

16. A pharmaceutical composition according to claim 15 further comprising an amount of the first and/or the second drug substance.

17. A pharmaceutical composition according to claim 15 or 16 for oral, parenteral, topical or nasal use.

18. A pharmaceutical composition according to any of claims 15-17, wherein the salt is dispersed in a dispersion medium.

19. A pharmaceutical composition according to any of claims 15-17, wherein the salt is dissolved in a solvent.

20. A pharmaceutical composition according to claim 19, wherein the solvent is an organic solvent or oil or a mixture thereof.

21. A pharmaceutical composition according to claim 19 or 20, wherein the salt or part of the salt – when the composition is diluted 1:5 such as 1:10, 1:20, 1:30, 1:40, 1:50, 1:60, 1:70, 1:80, 1:90 or 1:100 by volume with water at room temperature – precipitates.

22. A pharmaceutical composition according to claim 19 or 20 that forms a crystal suspension or precipitate upon contact with a body fluid.

23. A pharmaceutical composition according to claim 18, wherein the salt is suspended in a suspending medium.

24. A pharmaceutical composiiton according to any of claims 15-23 for parenteral use.

25. A pharmaceutical composition according ot any of claims 15-23 for topical use.

26. A pharmaceutical composition according to claim 25 in the form of a hydrogel.

27. A pharmaceutical composition according to any of claims 15-24 further comprising polylactic acid and/or polylactic-polyglycolic acid polymers.

28. A pharmaceutical composition according to any of the preceding claims, wherein the salt is selected from the group consisting of lidocaine-diflunisal and buvicaine-diflunisal.

29. A pharmaceutical composition according to any of the preceding claims comprising a first and a second salt according to any of claims 1-14 and wherein the first salt contributes to a relatively fast onset of action and the second salt contributes to a relatively prolonged duration of action upon administration of the composition.

30. A pharmaceutical composition according to claim 29, wherein the first salt is lidocaine-diflunisal and the second salt is bupivacaine-diflunisal.

31. Use of a salt according to any of claims 1-14 for the manufacture of a pharmaceutical composition for the treatment and/or relief of pain.

32. A method for treating and/or relieving pain comprising administering to a mammal in need thereof an efficient amount of a salt according to any of claims 1-14.

33. A method according to claim 32, wherein the pain is acute or chronic pain.

5

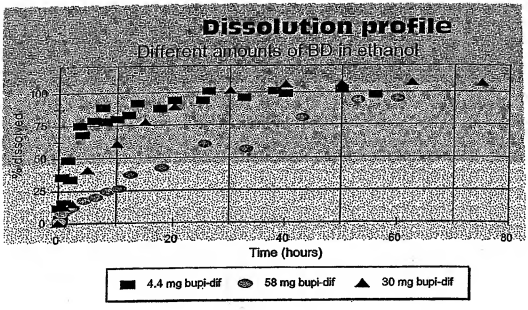

Dissolution profile
Different amounts of BD in ethanol
% dissolved
100
75
50
25
0
0
20
40
60
80
Time (hours)
4.4 mg bupi-dif
58 mg bupi-dif
30 mg bupi-dif

Fig. 1

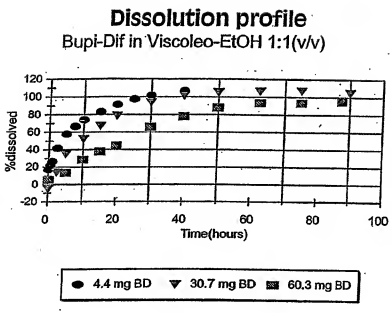

Dissolution profile
Bupi-Dif in Viscoleo-EtOH 1:1(v/v)
%dissolved
120
100
80
60
40
20
0
-20
0
20
40
60
80
100
Time(hours)
4.4 mg BD
30.7 mg BD
60.3 mg BD

Fig. 2

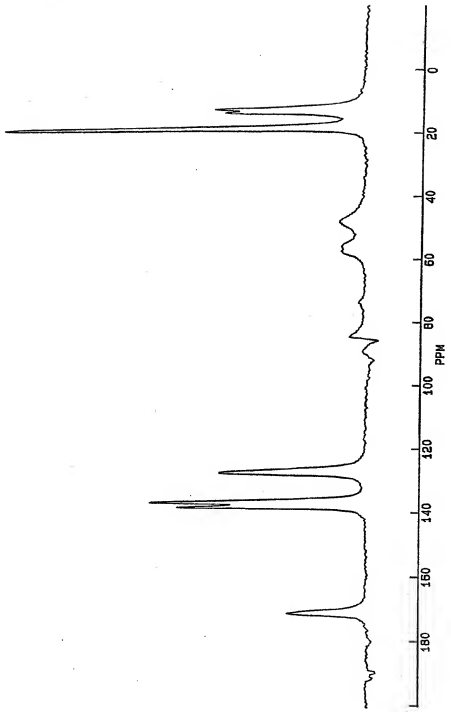


Fig. 3

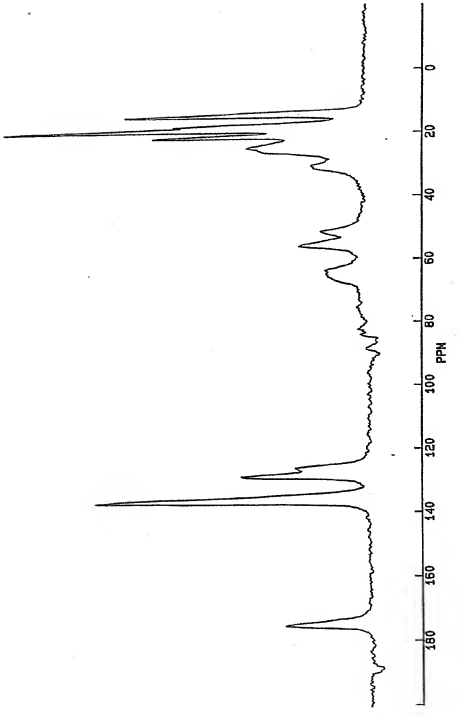


Fig. 4

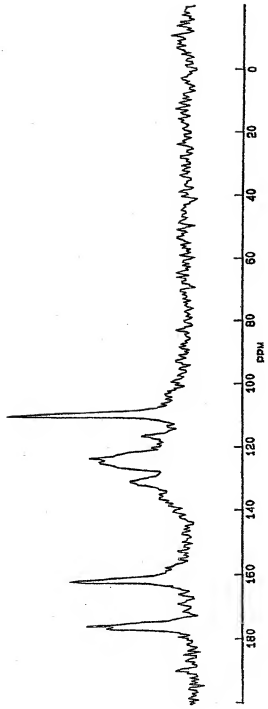


Fig. 5

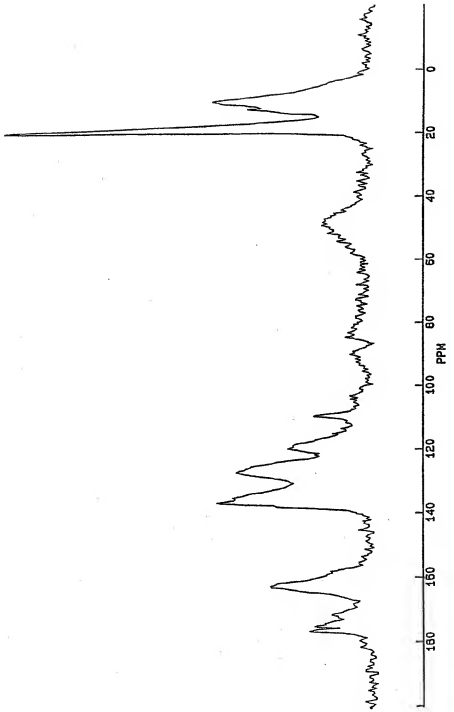


Fig. 6

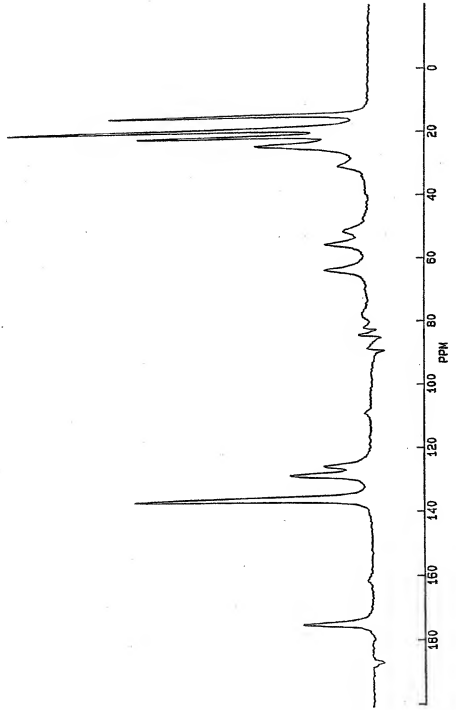


Fig. 7

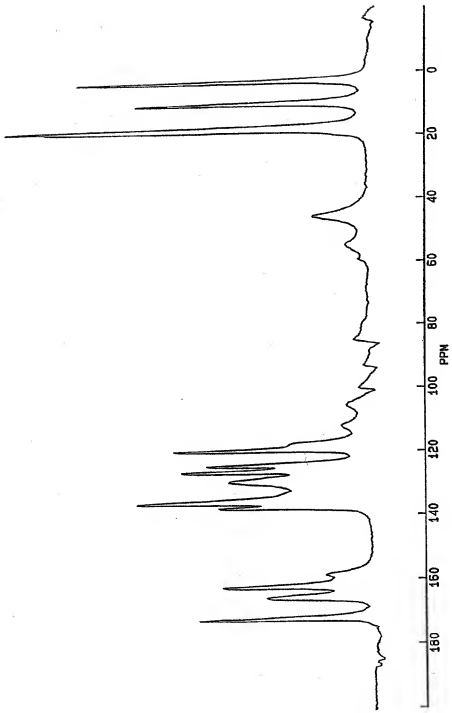


Fig. 8

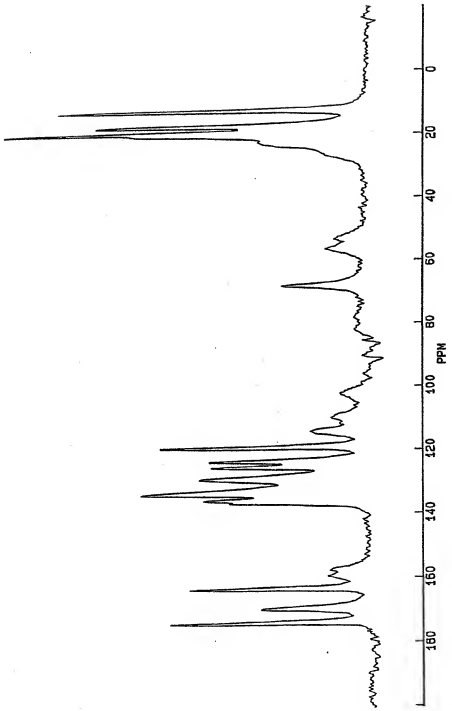
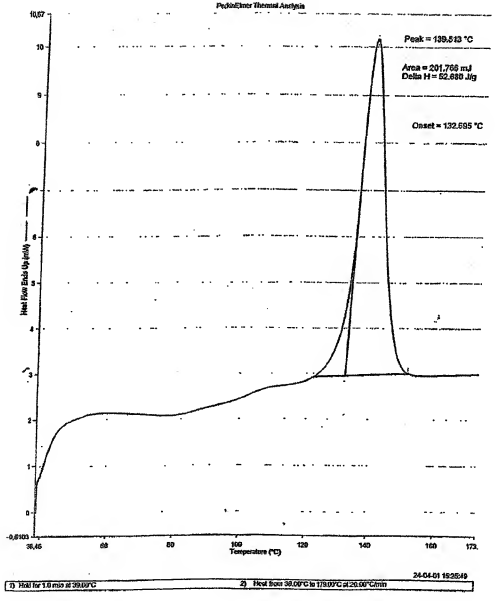


Fig. 9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Peak = 139,613 °C
Area = 201,766 mJ
Delta H = 52,889 J/g
Onset = 132,695 °C
Heat Flow Endo Up (mW)
Temperature (°C)
24-04-01 19:35:49
1) Hold for 1.0 min at 39.00°C
2) Heat from 39.00°C to 179.00°C at 20.00°C/min

Fig. 10

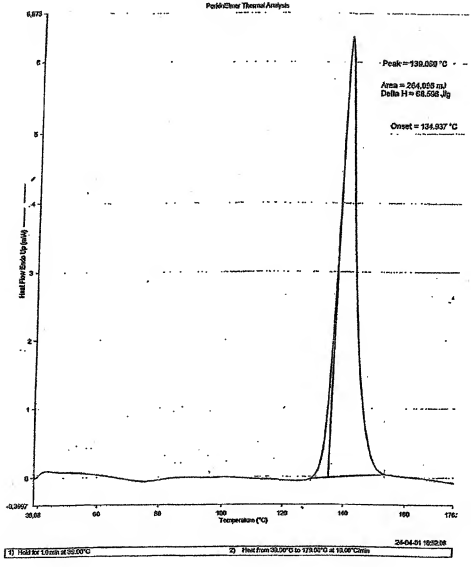
PerkinElmer Thermal Analysis
6,873
6
5
4
3
2
1
0
-0,2007
Heat Flow Endo Up (mW)
Peak = 139.089 °C
Area = 264.055 mJ
Delta H = 68.598 J/g
Onset = 134.937 °C
30,00
60
80
100
120
140
160
176,
Temperature (°C)
1) Hold for 1,0 min at 30,00°C
2) Heat from 30,00°C to 179,00°C at 10,00°C/min
24-04-01 10:02:28

Fig. 11

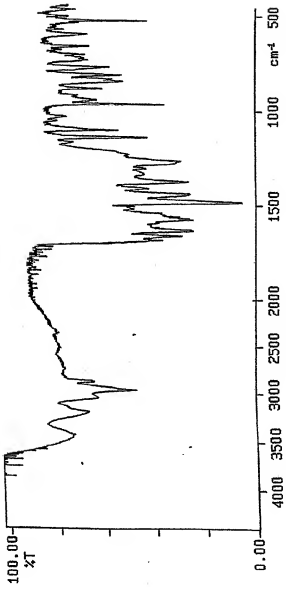

Fig. 12

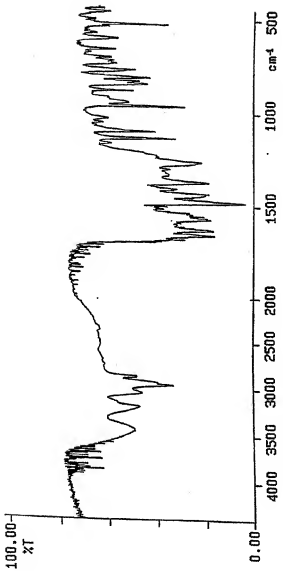

Fig. 13

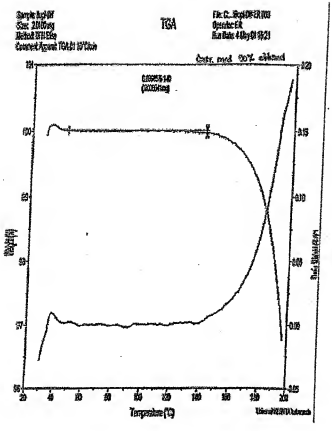

Fig. 14

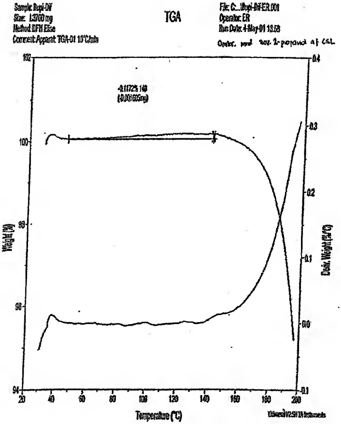
Sample: Bupi-DiF
Size: 1.3700 mg
Method: DFH Elise
Comment: Apparat TGA-01 10°C/min
TGA
Operator: ER
Run Date: 4-May-01 13:58
102
100
98
96
94
Weight (%)
0.4
0.3
0.2
0.1
0.0
-0.1
Deriv. Weight (%/°C)
20
40
60
80
100
120
140
160
180
200
Temperature (°C)

Fig. 15

INTERNATIONAL SEARCH REPORT

PCT/DK 03/00343

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/603 A61K31/445 A61K31/167

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 129 792 A (ESPINOS & BOFILL LAB SA) 23 May 1984 (1984-05-23) the whole document ---	1-31
X	DATABASE STN INTERNATIONAL [Online] File ZCA, ZCA accession no. 97:162816; PRODES S. A.: "Salt of indomethacin with N-(2-(diethylamino)ethyl)-5-(methylsulfonyl)-o-anisamide" XP002252103 & ES,A1,500026, 19820301 abstract ---	1-31
X	GB 1 291 386 A (SYNTEX CORPORATION) 4 October 1972 (1972-10-04) see especially example 14 the whole document --- -/--	1-31

X Further documents are listed in the continuation of box C.

X Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2003	12. 09. 2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	GÖRAN KARLSSON /EÖ

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/DK 03/00343

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERNATIONAL [Online] File ZCA, ZCA accession no. 70:11567; GALLARDO, ANTONIO, S. A.: "Organic salts of 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid" XP002252104 & ES,A1,341693, 19680701 abstract	1-31
X	DATABASE STN INTERNATIONAL [Online] File ZCA, ZCA accession no. 113:178288 ; CHINESE PEOPLE'S LIBERATION ARMY, GENERAL HOSPITAL OF JINAN MILITARY COMAND, PEOP. REP. CHINA : "Anti-inflammatory and analgesic gels containing indomethacin and topical anesthetics" XP002252105 & CN,A,1036327, 19891018 abstract	1-31
X	EP 0 250 802 A (MERCKLE GMBH) 7 January 1988 (1988-01-07) the whole document	1-31
X	DOUGLAS J. REINHART ET AL: "Postoperative Analgesia After Peripheral Nerve Block for Podiatric Surgery: Clinical Efficacy and Chemical Stability of Lidocaine Alone Versus Lidocaine Plus Ketorolac" REGIONAL ANESTHESIA AND PAIN MEDICINE, vol. 25, no. 5, September 2000 (2000-09) - October 2000 (2000-10), pages 506-513, XP002252102 the whole document	1-31
A	EP 0 637 448 A (ISCOFAR SAS) 8 February 1995 (1995-02-08) the whole document	1-31
A	GB 2 293 099 A (MAILWAY PACKAGING GROUP LTD) 20 March 1996 (1996-03-20) the whole document	1-31

INTERNATIONAL SEARCH REPORT

PCT/DK 03/00343

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 32-33
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 32-33

Claims 32-33 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

PCT/DK 03/00343

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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